REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 1-23, 30-34, 42 and 43 are pending after entry of the amendments set forth herein.

Claims 24-29 and 25-41 have been canceled above, without prejudice to the possibility of filing one or more continuing applications directed to the subject matter recited therein.

Claims 1-23 and 30-34 were examined. Claims 1-23 and 30-34 were rejected.

Applicant respectfully requests reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

The Telephone Interview

Applicant wishes to extend his appreciation to the Examiner for the courtesy provided to Applicants' representative during the telephone interview of June 1, 2007. During the interview, the Examiner indicated that he would reserve judgment until reading and considering further remarks made in this Office Action with regard to the grounds of rejection under 35 U.S.C. Sections 112, first paragraph, and 103(a).

This account is believed to be a complete and accurate summary of the interview as required by 37 C.F.R. § 1.133. If the Examiner believes that this summary is inaccurate or incomplete, Applicant respectfully requests that the Examiner point out any deficiencies in his next communication so that Applicant can amend or supplement the interview summary.

The Office Action

In the Official Action of April 17, 2007, the Examiner required cancellation of nonelected claims 24-29 and 35-41. In response thereto, Applicants have canceled claims 24-29 and 35-41 above, without prejudice to the possibility of filing one or more continuing applications directed to the subject matter recited therein.

Claims Rejected Under 35 U.S.C. Section 112, First Paragraph

Claims 1-23 and 30-34 were rejected under 35 U.S.C. Section 112, first paragraph as failing to comply with the written description requirement. The Examiner asserted that one of skill in the art cannot envision the detailed sequences of differential expression levels for the genus of disease processes. The Examiner further asserted: "The specification does not disclose a representative number of species of differential expression levels of disease[d] processes such that one of skill in the art would envision that applicant had possession of the full scope of the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it."

In response thereto, Applicant is not clear about what the Examiner has referred to as "it" when requiring "more than a mere statement that it is a part of the invention and reference to a potential method of isolating it." Applicant notes that the present invention is not directed to or claiming a method of isolating or identifying detailed sequences of differential expression levels for the genus of disease processes, or for any disease process, but rather to compare effects of different treatments on expression levels and correlate these to phenotypic responses across a plurality of diseased tissues that include the genes from which the expression levels are measured. To further clarify this, Applicants have amended independent claims 1, 21 and 30 to recite that the differential expression levels used are from predetermined genes of diseased tissue samples. For example, paragraph [0062] on page 23 of the specification notes that differential expression readings of diseased tissues versus a reference, which may be supplied from an already existing source.

Further, it is respectively submitted that Applicant is not claiming detailed sequences of differential expression levels for the genus of disease processes. Rather, Applicant is claiming a method of screening treatments to identify those treatments that may cooperate beneficially to treat a disease. Applicant is not claiming any particular sequence of differential expression levels, but rather a technique for identifying potentially useful treatments. Since Applicant is not claiming even one sequence of differential expression levels, it is respectfully submitted that it follows that Applicant cannot be properly considered to be claiming the genus of sequences of differential expression readings of diseased tissues, and that the current ground of rejection as lacking an adequate written description is inappropriate.

The Examiner referred to Paik, Molecular Profiling of Breast Cancer, Curr Opin Obstet Gynecol 18:59-63 (2006), interpreting this document to show that the correlation of expression of multiple genes

in combination on a microarray is not predictable. However, on page 61, column 2, last 7 lines, Paik notes that 16 cancer genes were selected from an examination of 250 genes by individual QRT-PCR and were normalized with five reference genes. A mathematical algorithm, called the Recurrence Score, was developed based on expression levels of the 16 genes and used to evaluate patients. It is respectfully submitted that this indicates predictability of the use of those 16 genes as an evaluation tool.

Further in support of this position, Applicant is submitting herewith an abstract from a scientific journal article by Levy, entitled "Microarray analysis in drug discovery: an uplifting view of depression", SCI STKE, 2003 Oct 28; 2003(206):pe46, that discloses: "Not only is microarray analysis a valuable tool for drug evaluation and leading candidate development, but the genes identified as markers for the various drug classifications point to new directions for research into the underlying pathways responsible for human diseases, such as depression and psychosis." It is respectfully submitted that this is evidence that there are currently known genes, the expression levels of which have been used in drug discovery.

Further, Applicant is submitting herewith an abstract from a scientific journal article by Debouck et al., entitled "DNA microarrays in drug discovery and development", Nat. Genet. 1999 Jan; 21 (1 Suppl):48-50, that indicates: "DNA microarrays can be used to measure the expression patterns of thousands of genes in parallel, generating clues to gene function that can help to identify appropriate targets for therapeutic intervention. They can also be used to monitor changes in gene expression in response to drug treatments."

Still further, Applicant is submitting herewith a scientific journal article by Lombardi, entitled "Industrializing microarrays: High-throughput microarray analysis can help improve drug discovery and development", Modern Drug Discovery, December, 2004, American Chemical Society. On page 47, column 1 of the article, it discloses "Microarray technology has already revolutionized significant parts of the drug discovery process, but with the development of HT arrays, pharmaceutical companies can now more wholly implement and apply the technology. For example, at the beginning of the process, HT technology can play a role in disease pathway identification and validation, and later on, once a target has been identified, in compound screening and lead optimization."

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1-23 and 30-34 under 35 U.S.C. Section 112, first paragraph, as being inappropriate.

Claims Rejected Under 35 U.S.C. Section 112, Second Paragraph

Claims 1-20 were rejected under 35 U.S.C. Section 112, second paragraph as being indefinite. The Examiner indicated that claim 1 is vague and indefinite because it is unclear whether the preamble, as written indicates whether it is the "combination of treatments" or the "disease process" that impacts gene expression. In response thereto, Applicant notes that the preamble recites that it is the "disease process" that impacts gene expression, which is why the phrase "that impacts gene expression" follows the phrase "disease process" and not the phrase "combination of treatments". Applicant believes therefore, that the preamble is clear and definite as written. However, now that the Examiner should be clear as to the meaning of the preamble, Applicant is open to suggestion by the Examiner of a change in wording that would help clarify the Examiner's understanding.

In view of the above remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1-20 under 35 U.S.C. Section 112, second paragraph as being indefinite, as being inappropriate, or, in the alternative, to suggest language that would satisfy the Examiner's needs.

Claims Rejected Under 35 U.S.C. Section 103(a) (Muraca in view of Glinskii)

Claims 1-4, 6-22 and 30-33 were rejected under 35 U.S.C. Section 103(a) as being unpatentable over Muraca, U.S. Publication No. 2003/0049701 in view of Glinskii, U.S. Publication No. 2004/0053317. The Examiner maintained this ground of rejection for the same reasons provided in the previous Office Action.

In responding to Applicant's arguments, the Examiner asserted that Muraca compares the phenotypic response signature of diseased tissues with signatures of differential expression levels of diseased tissues when untreated. The Examiner referred to paragraph [0023] of Muraca as support for his assertion. Applicant respectfully submits that paragraph [0023] of Muraca describes placing a plurality of tissues and/or samples at different, known positions on the substrate of a microarray. By dividing the samples into different groupings, the microarrays enable ultra-high-throughput molecular profiling. Applicant was unable to locate any description or suggestion in paragraph [0023] of generating a phenotypic signature as claimed.

In contrast, the present invention discloses generating a single phenotypic signature that includes the treatment response values of the plurality of diseased tissues. This signature, generated as a vector, is then compared to the phenotypic/genotypic signatures of the features. A phenotypic/genotypic

signature is generated by making a vector of the expression values for that feature (and the same respective feature on the other microarrays for the other diseased tissues) across all microarrays for the plurality of diseased tissues. It is respectfully submitted that neither Muraca nor Glinskii discloses or suggests generating either a phenotypic response signature or a phenotypic/genotypic signature as claimed.

The Examiner's comments about Applicant's characterization of the terms "a", "and" and "the" in the specification are not understood. Muraca does not disclose generating a differential expression level signature representing the differential expression levels for each diseased tissue sample. Nor does Muraca disclose generating a phenotypic signature representing treatment response values of each of the diseased tissue samples. It follows that Muraca does not disclose comparing these signatures, since Muraca does not disclose generating either type of signature.

New Claims

Independent claims 42 and 43 have been presented above. Claim 42 combines the recitations of claims 1 and 5 and further recites that the claimed signatures are provided as vectors. Claim 43 combines the recitations of claims 21 and 23 and further recites that the claimed signatures are provided as vectors. It is respectfully submitted that claims 42 and 43 are allowable over the art of record, and an indication to such effect is respectfully requested in the next Official Action.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10030208-1.

Respectfully submitted,

Date: 6/18/07

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1: Sci STKE. 2003 Oct 28;2003(206):pe46.

Microarray analysis in drug discovery: an uplifting view of depression.

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Genomic profiling provides insights into drug evaluation for diseases without defined molecular mechanisms or cellular assays. Levy provides a brief background in the development of microarray analysis and discussion of the application of this technique to pharmacogenomics. Highlighted is the microarray analysis of primary human neurons treated with antidepressants, antipsychotics, or opioid receptor agonists, demonstrating that these classes of drugs can be properly categorized by using two different statistical analysis methods: classification tree and random forest. Not only is microarray analysis valuable for drug evaluation and leading candidate development, but the genes identified as markers for the various drug classifications point to new directions for research into the underlying pathways responsible for human diseases, such as depression and psychosis.

PMID: 14583588 [PubMed - indexed for MEDLINE]

1: Nat Genet. 1999 Jan;21(1 Suppl):48-50.

DNA microarrays in drug discovery and development.

Debouck C, **Goodfellow PN**.

SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania 19406, USA.

DNA microarrays can be used to measure the expression patterns of thousands of genes in parallel, generating clues to gene function that can help to identify appropriate targets for therapeutic intervention. They can also be used to monitor changes in gene expression in response to drug treatments. Here, we discuss the different ways in which microarray analysis is likely to affect drug discovery.

PMID: 9915501 [PubMed - indexed for MEDLINE]

applicationsnotebook

Industrializing microarrays

High-throughput microarray analysis can help improve drug discovery and development.

BY STEVE LOMBARDI

With the completion of the Human Genome Project four years ago came the hope and promise that the world's most ambitious sequencing effort would revolutionize pharmaceutical research and, ultimately, give us better therapies and improved patient care. However, during the decade-long project, scientists learned that the genome is far more complex than previously thought. The first estimate of 30,000 genes has given way to estimates of hundreds of thousands of splice variants, millions of newly discovered transcripts, and tens of millions of genetic polymorphisms. But the tools needed to understand this level of complexity simply did not exist.

The microarray, invented in 1989 by Stephen P. A. Fodor and colleagues (*1–3*), has emerged as a central technology that is helping to unravel much of the genome's complexity. Over the past 15 years, microarray information capacity has consistently increased, providing for a tool that allows meaningful whole-genome analysis, currently able to measure expression for nearly 50,000 transcripts or genotype more than 100,000 polymorphisms in a single experiment. This broad-scale genetic analysis has not only helped to discover the underlying genetics for countless diseases, but has fundamentally improved drug discovery and development research.

Before whole-genome microarray analysis, many drug development assays were typically limited to answering a very focused question, often generating a single data point. To perform comprehensive drug discovery, researchers must answer hundreds or even thousands of different questions, making the process slow, expensive, and prone to variability.

Microarrays have offered a significant improvement by measuring thousands of data points in a single assay, with the ability to analyze changes in gene expression and DNA sequence variation across the whole genome. However, microarray throughput and cost-efficiency have limited their application in pharmaceutical research, which requires analyzing far more samples than does biomedical research.

High density. Affymetrix's high-throughput microarray plate, at left, contains 96 individual arrays mounted onto a single plate. Each of the 96 arrays contains the same content as a cartridge-based GeneChip Human Genome U133A Array, shown at right.

To enable industrialized microarray research, Affymetrix has recently developed an automated 96-array high-throughput (HT) format. The system automates the most labor-intensive steps in microarray processing—sample preparation, hybridization, washing, and scanning—dramatically reducing the cost per assay. This decrease in cost, increase in throughput, and added reliability make the HT system ideally suited for drug discovery and development applications, including target identification and validation, compound profiling, and improved clinical trial outcome.

Developing the HT array

The complexity of microarrays—requiring multiple enzymatic reactions, specific hybridization conditions, stringency washes, fluorescence scanning, and data analysis—presented a challenge for engineering the HT system.

The Affymetrix HT array adapts the same GeneChip technology and content to a standard 96-well plate footprint. Advances in feature size reduction have allowed significantly more content to be placed on smaller-sized arrays. And, by leveraging advanced automation methods, the HT system provides the consistency required to simultaneously analyze hundreds of high-content arrays.

The current HT microarray prototype contains 96 individual arrays mounted on a single plate, with each array containing the same genomic information as the company's Human Genome U133A array, but in approximately one-fifth the surface area. For each array of the 96-array plate, more than 500,000 probes are used to measure the expression of 18,400 human transcripts, meaning that each HT plate generates more than 48 million data points. By comparison, conventional HT screening may generate only a single data point per well—a total of 96 data points per plate.

Each 96-array plate is processed and analyzed on a robotic Array Station that automates the microarray processing workflow. This allows a high level of multiplexing in a single experiment and results in a significant decrease in sample-to-sample variation.

The small well size means that less sample can be used, as little as 100 µL per

hybridization, compared with the 150 µL required for corresponding cartridge-based experiments employing the same array size. With further optimization of array-packaging design, the reaction volume can be reduced to 30 µL or less, which will reduce cost accordingly. To process an equivalent number of samples on GeneChip cartridges, a lab not only would have to dedicate extraordinary labor resources but would require additional fluidics stations and multiple scanners as well—technologies that have been incorporated into a single HT microarray system. Modeling studies have determined that the automated system could process 20 plates or more per week, an equivalent of 1920 samples—previously an unimaginable thought for microarray analysis.

Applications to drug discovery and development

Microarray technology has already revolutionized significant parts of the drug discovery process, but with the development of HT arrays, pharmaceutical companies can now more wholly implement and apply the technology. For example, at the beginning of the process, HT technology can play a role in disease pathway identification and validation, and later on, once a target has been identified, in compound screening and lead optimization. Researchers can then use the HT microarray system to manage clinical trials, potentially expediting the delivery of new drugs to market.

HT array analysis provides researchers with a cost-efficient way to use genomewide expression profiling to identify drug targets and pathways for complex disease mechanisms. Additionally, GeneChip DNA analysis arrays have been used to discover the genetic basis of disease by mapping disease genes with whole-genome single nucleotide polymorphism (SNP) assays. The two platforms complement each other: Gene expression arrays identify differentially regulated genes from related individuals, and DNA analysis arrays can validate those differences in fine mapping experiments.

Once a disease pathway is identified, researchers need to validate it and verify that disrupting the pathway will actually affect the disease. Using whole-genome expression profiling, scientists can understand a wide range of effects—desirable and undesirable—that result from disrupting a pathway, and are then able to better evaluate a potential target for drug design. As researchers manipulate a large number of genes in the validation process, they can use HT arrays to simultaneously analyze the effects of each manipulation on global gene expression. Furthermore, the system can be used for microarray-based resequencing efforts to economically pinpoint disease-causing mutations and genetic variations in large clinical populations.

After identifying and validating a target, drug researchers can use HT arrays to screen libraries of compounds to identify those that disrupt expression of intended disease genes. Whole-genome expression analysis also identifies other changes in gene expression—such as "off-target" effects, some of which may suggest the compound produces far too many side effects to be effective.

Genetic and genomic analyses possible on a single 96-array plate containing microarrays manufactured at a given feature size

		Feature size	
Analysis type		**8 µm**	**5 µm**
Transcripts/genes	96 well	25,500	65,000
	Per plate	2,448,000	6,240,000
SNPs	96 well	14,000	36,000
	Per plate	1,344,000	3,456,000
Base pairs	96 well	70,000	180,000
	Per plate	6,720,000	17,280,000

For instance, if the changes in gene expression match those of a known toxin, the compound could be eliminated from the screening process early in development, saving both time and money. On the other hand, recording off-target changes in expression may help identify treatments for other diseases, operating through a different mechanism.

To perform comprehensive drug discovery, researchers must answer hundreds or even thousands of different questions.

Despite their development to treat hypertension and depression, the respective successes of Viagra for erectile dysfunction and Wellbutrin for smoking cessation are prime examples of exploiting off-target drug action to serve other therapeutic markets.

More successful clinical trials

By providing more complete genetic and genomic information, microarrays are helping researchers classify disease markers, predict drug efficacy, and more successfully manage clinical trials. While the throughput and cost-efficiency of the HT system are key to industrializing microarray technology, there are already more than 40 examples of microarrays being used in large-scale trials.

For example, a recent Phase III clinical trial by Novartis Pharmaceuticals used expression profiles to predict the success or failure of Glivec/Gleevec treatment on chronic myelogenous leukemia (*4*). Researchers analyzed gene expression patterns from patients prior to treatment and found a 31-gene "no response" signature, which predicts a 200-fold higher probability of failed therapy.

Similarly, in a Phase II clinical trial conducted at the Dana Farber Cancer Research Institute for Millennium Pharmaceuticals' drug Velcade, researchers used GeneChip arrays to collect pharmacogenomic data from myeloma patients treated with the drug (*5*).

The scientists discovered a pattern consisting of 30 genes that correlate with response or lack of response to therapy. Clinical utility of biomarkers will be further assessed in a Phase III trial.

While much progress has already been made using gene-expression analysis, studies to identify genes associated with drug response, efficacy, and toxicity may become one of the most promising applications for whole-genome DNA analysis. Tools like the GeneChip Mapping 100K Array Set (which can genotype more than 100,000 SNPs distributed across the genome) now allow researchers to readily genotype large populations of responders and nonresponders to a given drug for phenotypes including efficacy and toxicity.

With these kinds of genetic studies, scientists hope to elucidate the genes contributing to variable drug response. In key Phase III trials, microarray genotype analysis could be used to stratify patient populations to eliminate poor or toxic responders. Such stratification would help ensure maximum effectiveness through clearer statistical differentiation between drug and placebo, while also reducing trial size and costs, and improving the odds of drug approval.

Once a drug is on the market, patient stratification could also be used to accelerate drug expansion into new indications through faster, smaller, and more definitive Phase IV trials or to establish medical superiority of a late-to-market drug relative to entrenched competitors in an important class of patients. Genomewide genotype information will also fuel future research. By better understanding genetic mechanisms of drug response in patients, researchers will have made significant progress on finding next-generation drugs.

The way ahead

As microarray technology advances and more content can be placed on smaller-sized arrays, the application of HT microarray systems to pharmaceutical development will become even more significant and extend beyond the traditional genetic and genomic experiments.

The ability to use microarrays representing the complete coding content of the human genome—more than 47,000 transcripts—will help accelerate discovery even further. Human transcriptome analysis (i.e., the complete collection of transcribed elements of the genome) is also made possible by the HT system, where an experiment can now be constructed to analyze an entire genome for structure–function relationships on a single plate.

Similarly, advances in genotype analysis will be accelerated by microarrays that can analyze more SNPs and can sequence larger parts of the genome. With just two technicians running 10 plates per week, the throughput afforded by HT analysis allows for previously inconceivable experimental scale (see the table): 960 whole-genome expression profile scans, 2.5 complete human transcriptome scans (with probes positioned every 5 base pairs), or analysis of nearly 35 million SNPs.

Efforts such as these are helping researchers use the genome sequence to improve pharmaceutical R&D and develop new therapies for improved disease management. While the benefits of HT array analysis are only beginning to be realized, with the care taken to fit this technology into existing infrastructures, it offers the prospect of more efficient, cost-effective, and personalized approaches to patient care.

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(4) McLean, L. A.; Gathmann, I.; Capdeville, R.; Polymeropoulos, M. H.; Dressman, M. *Clin. Cancer Res.* **2004**, *10*, 155–165.

(5) Mulligan, G.; et al. Pharmacogenomic analyses of myeloma samples from bortezomib (Velcade) Phase II clinical trial. Poster and abstract presented at the American Society of Hematology Annual Meeting, Philadelphia, 2002.

Steve Lombardi is senior vice president for commercial operations at Affymetrix. □

Flu trials, *from p. 45*

comes during a pandemic. But the world's total vaccine production is currently limited to about 235 million doses, WHO says. To begin to approach the challenge of proactively defending against a pandemic, researchers are showing increasing interest in using an adjuvant to boost the immune activity of flu vaccines.

Chiron's H9N2 NIAID contract specifies production of vaccine both with and without the company's MF59 adjuvant. This way, says Linda Lambert, who heads up the NIAID influenza research program, "we can determine if the adjuvant significantly augments the protective effects of the vaccine, enabling us to use lower doses and thereby extend the vaccine supply."

A Phase I clinical trial carried out by British health authorities and Chiron in 2001 showed MF59 boosted the antibody response from a vaccine designed against H5N1 (*Lancet* **2001**, *357*, 1937–1943). In a more recent study of 200 adult volunteers, GlaxoSmithKline researchers found that alum—an aluminum-based adjuvant that is notably less expensive than MF59—augmented a live attenuated vaccine's effect enough to require only about 13% of the current conventional flu vaccine dose to stimulate high levels of immunoprotectants.

> "There is increasing concern around the world that an influenza pandemic, which could have disastrous consequences for public health, is imminent."

All this research in the name of pandemic matters will likely circle its way back to aiding the needs of the annual vaccine supply problem. And, in turn, the current seasonal shortage is fueling interest and concern for the pandemic issue. This is all underlined by the ever-present fear of terrorism, because pandemic flu strains are considered by many to be potential biowarfare agents. The intensity of flu clinical research seems to be taking an upward swing. □